UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,134	07/23/2003	Redford B. Williams JR.	5405.239CT	8271

20792 7590 07/05/2006

MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

EXAMINER	
SITTON, JEHANNE SOUAYA	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/625,134	WILLIAMS, REDFORD B.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/31/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, newly added claims 17-26 are pending in the instant application. Claims 1-16 have been canceled. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are newly applied, as necessitated by amendment. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

Priority

2. Applicant's claim for benefit of priority from application 60/162,390 is acknowledged. However, the claims have not been awarded the benefit of the filing date of the '390 application because the claimed subject matter is not present in the '390 application. Although the '390 application states that assessing genotypes of a polymorphism of the promoter region of the serotonin transporter can identify persons who are more sensitive to stress, the '390 application does not set forth any method of identifying subjects having an "increased likelihood of having an increased sensitivity to stress" nor does the application teach or recite "the presence of at least one serotonin transporter gene promoter long allele identifies the subject as having an increased likelihood of having an increased sensitivity to any stress [or broadly "any physiological response to any stress"]" as is broadly encompassed in the newly added claims. The '390 application is directed to an association between diseases, such as cardiovascular diseases, and presence of the short allele of the serotonin transporter gene promoter, preferably two copies of the short allele. The '390 application does not demonstrate an association between

cardiovascular diseases, in response to stress and the long allele of the serotonin transporter gene promoter.

Claim Rejections - 35 USC § 102

3. Claims 17-19 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Arinami et al., (Thrombosis Haemostasis, vol. 81, pp 853-856, June 1999) as defined by Grassi et al (Circulation, vol 90, pp 248-253, 1994).

The claims are drawn to a method of screening subjects for increased likelihood of having an increased sensitivity to stress, having increased physiological response to stress, or developing a cardiovascular disease associated with an increased physiological response to stress, by determining the presence of at least one serotonin transporter long allele in a subject wherein the presence of at least one long allele serotonin transporter gene promoter genotype indicates that said subject is at increased likelihood of having an increased sensitivity to stress, having increased physiological response to stress, or developing a cardiovascular disease associated with an increased physiological response to stress.

Arinami teaches analyzing patients with coronary artery disease for a serotonin transporter gene promoter polymorphism (see abstract, pp 853-854). Arinami teaches that the L allele (the long allele) was observed more frequently in patients with coronary heart disease ($p < 0.03$) and that this association was stronger ($p < 0.003$) in patients that also smoked. The specification defines stress as any physical or psychological stimulus that induces a physiological stress response in a subject (e.g. increased heart rate, increased blood pressure...). As defined by Grassi et al (abstract, col. 1, lines 18-22) smoking markedly and significantly increased mean

arterial pressure, heart rate, calf vascular resistance, and plasma norepinephrine and epinephrine levels. The teachings of Arinami teach a study which identifies subjects with at least one serotonin transporter long allele as having "increased likelihood" of having increased sensitivity to stress (smoking) and an increased physiological response to stress (physiological effects of smoking) and developing a cardiovascular disease associated with an increased physiological response to stress (CAD), and therefore, the teachings of Arinami anticipate the instantly claimed invention.

Response to Arguments

4. Arguments with regard to priority and the rejection under 35 USC 102(b) will be addressed together. The response at pages 4-5 cites the Summary of the '390 application as support for the claimed subject matter. This argument as well as this section of the '390 application have been thoroughly reviewed but were not found persuasive. The Summary states "The present invention is based on the recognition that by assessing genotypes (long vs. short) of a polymorphism of the promoter region of the gene that encodes serotonin transporter (5HTTLPR), once can identify persons who are more sensitive to stress and, therefore at higher risk of developing a broad range of diseases". The Summary then goes on to specifically state "In one particular embodiment, the method comprises determining the presence of **at least one (and preferably two) serotonin transporter gene promoter short alleles... indicates that said subject is at increased risk of disease, as compared to a subject with no short alleles or a subject with only one short allele**". No alternative embodiment is set forth. Therefore, this section of the Summary makes the opposite conclusion as that encompassed by the claimed

invention. The response asserts that the recitation regarding detection of the short allele is set forth as only one embodiment, and that one of skill would reasonably conclude that the invention is directed to identifying either a short or long allele genotype and identifying an association with either genotype. This was not found persuasive because while detecting at least one short allele encompasses detecting one long allele, the recitation of "preferably two short alleles" as well as the statement of comparison, are directed to comparing two short alleles vs one short or no short alleles and specifically excludes an increased risk association with one or two long alleles as is presently encompassed by the claims, directing comparison to two short alleles as increased risk over one short (one long) or no short. While the '390 application teaches to detect the polymorphism, either long or short, it makes absolutely no statement or conclusion either in the specification or the claims regarding an increased risk of "increased sensitivity to stress", "increased physiological stress response" or "developing a cardiovascular disease" by detecting "at least one serotonin transporter gene promoter long allele" as is recited in the instantly pending claims. In fact, the '390 application makes the opposite assertion, thus not making it reasonably apparent to one of skill in the art that the instantly pending claims are supported by this disclosure in the '390 application.

The response asserts that the '390 application provides data to demonstrate an association between the long allele genotype and increased sensitivity to stress as presented in Example 1 at pages 4-5 of the '390 application. This argument has been thoroughly reviewed but was not found persuasive. While the '390 application teaches that subjects with high 5-hydroxyindolacetic acid levels differed from low levels on measures such as higher basal plasma prolactin, decreasing plasma cortisol, larger heart rate and blood pressure, the '390 application

makes no conclusion regarding sensitivity to stress. The only conclusions made are that "5HTTLPR genotype data ... revealed higher CSF 5HIAA levels in subjects with l/l or l/s genotype" that "genotype data indicate that cardiovascular and cortisol reactivity levels correlate the presence of one or more alleles", and "long allele acts as an autosomal dominant in regulating 5HIAA levels" however the specification does not teach or assert that this is taken as "an *increased* sensitivity to stress" or "*increased* physiological response to stress" or explain why it would be taken as such nor does it correlate such data with regard to any specific levels (ie: increased vs decreased) of sensitivity. With regard to increased physiological response, cortisol levels are known to increase in response to stress, whereas the example teaches that cortisol levels were decreased during the protocol. This appears to indicate reduced response, not increased response. This data coupled with the teaching of the detection of **two short** alleles and an association to disease risk set forth in the '390 specification, one of skill in the art would not be apprised of the instantly pending claims. The '390 application, taken as a whole provides preliminary results regarding genotypes, 5-HIAA levels, and heart rate, cortisol, prolactin, and blood pressure levels and asserts an association between two short alleles and increased risk of disease. Accordingly, one of skill in the art would not be able to make the claimed conclusions from such preliminary and contradictory information set forth in the provisional application. The instantly filed claims are not supported under 35 USC 112/first paragraph by the '390 application. Accordingly, the rejection set forth under 102(b) is proper and the declaration submitted under 1.131 cannot be used to overcome the rejection.

5. Claims 17, 18, 20 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Hanna (Hanna et al; Neuropsychopharmacology, vol 18, February 1998, pages 102-111).

Hanna teaches that subjects were analyzed for blood 5-HT levels and that the 5-HTT genotype was analyzed for association with seasonal variation (stress) (see page 108, col. 1). Hanna teaches that subjects with the ll genotype for 5-HTT transporter had significant seasonal differences in blood 5-HT levels whereas subjects with the ls genotype did not (increased sensitivity to stress, physiological response to stress) (abstract, page 107, para bridging cols 1 and 2).

Claim Rejections - 35 USC § 112

Enablement

6. Claims 17-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening human subjects for increased risk of coronary heart disease in response to smoking by detecting the presence of at least one serotonin transporter gene promoter long allele, does not reasonably provide enablement for a method of identifying any subject, from any species, having an increased likelihood of having an increased sensitivity to any stress or any increased physiological response to stress or increased likelihood of developing any cardiovascular disease associated with an increased physiological response to stress by detecting the presence of at least one serotonin transporter gene promoter long allele. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Nature of the Invention and the breadth of the claims.

The claims are broadly drawn to identifying any subject, including from any species, of having increased likelihood of having an increased sensitivity to any stress or any increased physiological response to stress or increased likelihood of developing any cardiovascular disease associated with an increased physiological response to stress by detecting the presence of at least one serotonin transporter gene promoter long allele. The specification further broadly defines "stress" as any physical or psychological stimulus that induces a physical stress response (see p. 4, lines 29-32).

It is noted that although the specification is silent with regard to coronary heart disease (CHD), smoking, and the serotonin long allele, the art (Arinami et al; Thrombosis Haemostasis, vol. 81, pp 853-856, June 1999) is enabling for a method of screening human subjects for increased risk of CHD in response to smoking by detecting the presence of at least one serotonin transporter gene promoter long allele.

Amount of Direction and Guidance and presence and absence of working examples:

The specification asserts that the method of the invention comprises determining the presence of at least one, and preferably two serotonin transporter gene promoter long alleles in a subject and that the presence of at least one and particularly two long alleles indicates the subject is at increased risk of disease as compared to a subject with no long alleles or with only one long allele (page 2). The specification teaches analyzing human subjects, not including those with medical or psychiatric disorders or current medication use, for 5HIAA levels (primary serotonin metabolite) in response to tryptophan depletion and response to the antagonist pindolol. The specification further analyzes differences in biological responses to tryptophan depletion or infusion, such as heart rate, mean arterial pressure, epinephrine and norepinephrine levels, cortisol levels, and prolactin levels in subjects with either short or long serotonin transporter gene promoter polymorphisms.

With regard to claims 17 and 18, the specification teaches varying levels in heart rate, mean arterial pressure, epinephrine and norepinephrine levels, cortisol levels, and prolactin levels in subjects with the short and long serotonin transporter gene promoter polymorphisms in response to the following stressors: reading text aloud, anger recall, sadness recall (page 7-8). The results of such analysis, were widely varied. For example, Figures 4-7 show that larger mean arterial pressure and heart rate changes are found in subjects with the at least one l allele. However, other differences in physiological response are not correlated. For example, the pattern of epinephrine response changes does not appear to differ significantly between ss or ls and ll individuals (see Figure 8). In many instances, there is significant overlap in ranges. The

same patterns are found for norepinephrine (see figures 10 and 11). Although the specification asserts "there does appear to be a tendency for those with l alleles or high 5-HIAA to have higher SNS outflow", there is no indication if this trend is statistically significant. Upon careful examination of figures 10-13, the "trend" that is discernable appears to be for figure 12 only, however it is not supported by the data in figure 10 as both ss vs ls and ll patterns change. Accordingly, no change or increase in sensitivity appears predictable from such data. Further, while cortisol levels are known to increase in response to stress, subjects with the ss genotype and high 5HIAA level subjects exhibited higher cortisol levels during the stress protocol and active tryptophan depletion. This appears to contradict what one would expect given the assertions and guidance given in the specification. Further, the similarity in cortisol levels for the ss genotype and high 5HIAA levels contradicts the assertions made in the specification regarding the associations of the ll or ls genotype with high 5HIAA levels vs the ss genotype and low HIAA levels. The specification provides no guidance as to how to interpret this conflicting data regarding "increased sensitivity" or "increased physiological response". With regard to prolactin levels, the interpretation of Figures 24-27 is unclear. Prolactin levels are known to increase in response to stress. However, in figures 24 and 26, subjects with high 5HIAA levels and subjects with at least one l allele had higher prolactin levels, which would be expected in response to stress, than subjects with low 5HIAA levels and subjects with the ss genotype. Further, for both ll or ls vs ss subjects, prolactin levels appeared to increase following a stress period. It is unclear, however if this is an indication that subjects with low 5HIAA levels or the ss genotype are more sensitive (greater changes in levels) or less sensitive to stress? The specification does not provide any guidance other than to describe the figures. With regard to

figures 28-34, some figures show almost no change for either hi or low 5HIAA levels (figure 28), whereas other figures show greater changes in expression of adhesion molecules for subjects with low 5HIAA levels (figures 29-32). Figure 33 and 34 shows that changes occurred for all alleles detected, but the significance of such parameters with regard to "increased sensitivity to stress" or "increased physiological response to stress" and promoter genotypes is not apparent.

The specification does not provide any examples of an association between the presence of any of the claimed diseases and subjects with the long allele serotonin transporter gene polymorphism. Thus, while the study provided in the specification illustrates that subjects with different serotonin transporter gene promoter alleles have different biological responses to tryptophan infusion or depletion, the specification does not analyze the association between the presence of any of the claimed diseases and the long allele of the serotonin transporter gene promoter in subjects either in the presence or absence of a response to stress. It would essentially be an unpredictable trial and error process to determine whether subjects with the long allele of the serotonin transporter gene promoter polymorphisms were in fact at an increased risk for developing any of either the broadly claimed diseases.

The specification has no working examples, whatsoever, of any studies or methods that associated the presence of any cardiovascular disease in general, or of the claimed diseases, or sensitivity to stress or increased physiological response to stress in non human subjects with at least one long allele of the serotonin transporter gene promoter.

Level of predictability and unpredictability in the art

The art teaches that an association between the serotonin transport gene promoter alleles and different diseases is unpredictable. For example, Persico (Persico et al; American Journal of Medical Genetics, vol. 96, pp 123-127, 2000) teach that family based studies provide conflicting evidence of linkage or association between either the short or the long allele of the serotonin transporter gene promoter in subjects with autistic disorder (see abstract) despite the fact that elevated serotonin blood levels have been consistently found in approximately 30-50% of autistic patients (see p. 123, col. 1, 2nd para). Further, Kunugi (Kunugi et al; American Journal of Medical Genetics, vol. 96, pp 307-309, 2000) teach that while two independent research groups consistently reported a significant association between the serotonin transporter gene promoter short allele and late onset sporadic Alzheimer's disease, Kunugi could not find an association between such an allele and either early or late onset Alzheimer's disease in a Japanese population.

Further, the post filing date art demonstrates the unpredictability of serotonin promoter alleles and stress. For example, while Rozanski teaches that depression contributes to coronary artery disease (Rozanski et al; Circulation, vol. 99, pages 2192-2217; 1999, see abstract), Kendler (Kendler et al; Arch. Gen. Psychiatry, vol. 62, May 2005, pages 529-535) teaches a study which analyzed the association between serotonin transporter promoter short and long alleles, stressful life events, and depression. Kendler teaches that individuals with two short alleles had an association between low threat event stress and depression. In contrast, Rozanski (Rozanski et al; Circulation, vol. 99, pages 2192-2217) teaches that depression contributes to coronary artery disease (see abstract).

Additionally, applicants own post filing date art (Williams et al; Neuropsychopharmacology, 2003, vol. 28, pages 533-541) teaches an analysis of CNS serotonergic function and serotonin related gene polymorphisms, including serotonin transporter promoter short and long alleles, and teaches that the effects of serotonin related gene polymorphisms on CNS serotonergic function vary as a function of both ethnicity and gender. Further, Williams teaches that the ss genotype is associated with higher 5HIAA levels in African Americans, but with lower levels in Caucasians. Williams teaches that the ss genotype is associated with higher 5HIAA levels in women but with lower levels among men (page 539, col. 1). Accordingly, the correlation between 5HIAA levels and serotonin promoter polymorphism genotype is not as predictable as asserted in the specification. Williams specifically teaches that "Further research will be required to determine the mechanisms underlying these differential effects. In the meanwhile, both ethnicity and gender should be taken into account in research evaluating effects of these and related polymorphisms on CNS serotonergic function, as well as the broad range of biological and behavioral functions that are regulated by CNS serotonergic function." (see abstract). The instant specification, however, provides no assessment as to ethnicity or gender with regard to the data presented and fails to support the broad scope of the claims directed to "any" subject.

With regard to other species, Wurtman (Metabolism Clinical and Experimental, vol. 54, pages 16-19, 2005) teaches mice with SS or SL alleles exhibited greater stress induced increases in plasma adrenocorticotropic hormone levels than LL animals, which does not support the scope of the broadly claimed invention. The instant specification, however, provides no teaching or

guidance with regard to promoter polymorphism in other species and stress sensitivity, physiological stress response, or cardiovascular disease risk.

Thus the art not only fails to support the efficacy of the invention, but in fact, supports the unpredictability of associating serotonin transport gene promoter alleles and different diseases (even diseases which were previously found to be associated with one of the alleles), stress, and CNS serotonergic function.

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of Experimentation necessary

The quantity of experimentation in this area is extremely large since the claims are broadly drawn to detecting an increased sensitivity to any type of stress, any increased physiological stress response, and to a broad category of cardiovascular diseases and the specification does not support the scope of the broadly claimed invention. Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher*, F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the unpredictability in the art. Furthermore, the Court in *Genetech Inc. V Novo Nordisk*

42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

To be able to practice the invention as broadly as it is claimed, that is to determine that a subject is at an increased risk for an increased sensitivity to any type of stress, or any increased physiological response in response to stress or to any cardiovascular disease associated with an increased physiological response to stress based on the presence of at least one long allele of the serotonin transporter gene promoter, the skilled artisan would have to perform a large number of studies, that included a sufficient number of subjects form different populations and species, exposed to different types of stress as well as measuring different physiological responses, and subjects suffering from different types of cardiovascular diseases as well as a sufficient number of control subjects, to determine if in fact, a subject could be determined to be at an increased risk for developing any type of disease, in response to stress or not, or the diseases claimed, based on that subject having at least one long allele of the serotonin transporter gene promoter polymorphism.

Given the conflicting guidance with regard to physiological responses to stress in the specification as well as the lack of guidance from the specification regarding disease risk, and the unpredictability taught in the art, such a study would be replete with trial and error analysis, the results of which are unpredictable. There is no teaching in either the specification or the art that the long allele of the serotonin transporter gene promoter is associated with *any* cardiovascular disease, such as vascular diseases, hypertension, hypotension, or aneurysms. These diseases each represent a large category of different disorders and diseases, wherein in many cases, each disease in the large category are involved with different biological mechanisms and genes and

are associated with different risk factors and response to therapies. The specification merely provides an invitation for further experimentation and the claims are broadly drawn to methods that basically represent a research project, such research project requiring extensive trial and error analysis and which results are unknown and unpredictable, as illustrated by the state of the art at the time of filing.

Conclusion:

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to make or use the methods of the claims as broadly written.

Response to Arguments

7. The response traverses the rejection. The response asserts that the claims are enabled by the specification and cites examples 2-6. This argument has been thoroughly reviewed but was not found persuasive for the reasons set forth in the rejection. Although the examples set forth different biological responses to stress, the significance of such data with regard to the instantly pending claims is not clear. Further, given the contradictory examples set forth in the art, including applicant's own post filing date work with regard to genotype and 5HIAA levels, the specification does not appear to provide enablement for the broad scope of the claims. The

response further asserts that the specification is enabled for the identification of a subject having an increased likelihood of developing a cardiovascular disease associated with an increased physiological response to stress on the basis that it was well known that cardiovascular disease and risk factors associated with cardiovascular disease are associated with an increased physiological response to stress and cites a number of different references. This argument as well as the cited references have been thoroughly reviewed but were not found persuasive. Although there are some physiological stress responses that are associated with cardiovascular disease risk, the mechanisms by which such occurs is not completely understood, nor is the association between cardiovascular diseases and serotonin transporter promoter polymorphism. For example, with regard to Rozanski, although Rozanski teaches that depression is a psychosocial domain which is associated with CAD, Kendler teaches that individuals with two short alleles had an association between low threat event stress and depression. With regard to Everson et al 1999, Everson discusses anger expression and stroke risk but teaches that suppressed anger and controlled anger were not consistently related to stroke risk. The differences in expression of anger, however, are not necessarily predictive of stress sensitivity nor does Everson 1999 address such. With regard to Karmarck et al, although Karmarck addresses blood pressure responses during mental stress and atherosclerosis, Karmarck teaches a number of limitations with regard to the study, including the population and the generalizability of the findings and the fact that all the subjects were male and ethnically homogenous. Further, none of the cited references, including Everson et al 2001 or Matthews et al provide any assessment regarding the risk of disease in response to physiological stress response with regard

to the serotonin transporter long allele polymorphism. For these reasons and the reasons already made of record, the rejection is maintained and newly applied to the newly added claims.

8. Claims 19 and 22-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claim 19 recites "having increased likelihood of developing a cardiovascular disease *associated* with an increased physiological response to stress". The response asserts that support can be found in the originally filed claims and in the specification, but provides no specific citation. The originally filed claims were drawn to detecting disease risk "in response" to stress. The specification also sets forth methods of detecting disease risk "in response" to stress. However, the term "associated" is broader in that it not only encompasses a cause and effect relationship such as "response" but also encompasses correlations which are not necessarily cause/effect but rather could be occurring concurrently, and not necessarily a response to stress. The specification does not provide support for such and accordingly, the newly filed claims appear to introduce new matter into the claimed invention.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton
Primary Examiner
Art Unit 1634
6/23/06